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mRNA: vaccine or gene therapy? Regulatory issues.

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Abstract

Vaccines escape some of the controls required for human drugs (without scientific justification). However, mRNA vaccines, which represent a new class of vaccine, should be subject to more controls than conventional vaccines because they are based on several new technologies. Conventional vaccines could be replaced by mRNA vaccines and anti-cancer "vaccines" (actually therapies) are being announced. Moreover, mRNA vaccines can be considered as pro-vaccines (the injected substance is not the active substance).

The WHO tried unsuccessfully to regulate these new products in 2022. mRNA vaccines are not subject to regulation as gene therapy products (GTP) although they correspond to the definition of GTP and although for the EMA therapeutic mRNAs are considered as gene therapy products. Moreover, Moderna and BioNTech expected their products to be regulated as gene therapies.

Therefore, anti-covid mRNAs are subject to the EMA's human drug regulations, which also apply to vaccines; there is even an EMA document that requires pharmacokinetic testing for DNA vaccines. The exclusion of anti-Covid mRNAs from the regulation of gene products is not justified by the regulatory agencies, which allows these products to avoid numerous controls, in particular concerning specific toxicity, integration in the genome, transmission in the germ line, toxicity linked to the expression of structurally altered proteins, reproductive toxicity, repeated toxicity and excretion in the environment.

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Introduction

The regulation of drugs and vaccines is a poorly understood yet very important subject.

Indeed, health products must undergo very strict controls in principle to control their efficacy and safety profile. Vaccines have been exempt from some of these controls for a long time without any real scientific justification. However, mRNA vaccines, which represent a new class of vaccine, should be subject to more controls than conventional vaccines because they are based on several new technologies.

This is all the more true since manufacturers are planning to replace certain "classic" vaccines with mRNA vaccines, starting with influenza vaccines: Indeed, Sanofi is launching the clinical trial of the first mRNA-based seasonal flu vaccine candidate [1] and Moderna has many mRNA vaccines in clinical trials (Covid, influenza, Human metapneumovirus, parainfluenzae, RSV, HCoV, CMV, EBV, HSV, varicella, Herpes, HIV, Zika, Nipah) particularly the phase 3 trial of the flu vaccine [2]. For these flu vaccines, emergency approval should not apply and the requirement for these additional studies should not be exceeded.

In addition, cancer "vaccines" are being announced (e.g. Moderna &Merck are partnering in trials of mRNA-4157/V940, an anti-melanoma "vaccine" combined with Keytruda (a monoclonal antibody directed against the programmed cell death receptor (PD-1) and acts by enhancing the ability of the body's immune system to detect and fight tumor cells, by blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating the anti-T cell response, particularly antitumor. [3]

We must be very vigilant about the term vaccine associated with therapeutic drugs, particularly with regard to the regulations that apply to them.

Definitions: pro-vaccine, pro-drug, pharmacokinetics

mRNA vaccines can be considered as pro-vaccines; this is a neologism modelled on the word pro-drug which designates a drug which, after administration, is converted by the organism into a pharmacologically active drug. In fact, according to the principle of mRNA, this must be translated into protein by the cells of the person vaccinated (the injected substance is not the substance causing an active immunization).

According to the FDA[4], mRNA vaccines would correspond to the typeIA of pro-drug which corresponds to substances converted by the cells into active drug (and which include nucleoside analogues of antivirals). The FDA points out the particular problems of pro-drugs concerning the complete or incomplete conversion into an active substance and the question of toxicity: how the pro-drug contributes significantly to the toxicity profile of the active drug and in particular according to the site of transformation and action. For mRNA vaccines, biological transformation occurs in many cell types and in all organs, whereas the desired goal, i.e. immunization, will only occur in immune cells.

In general, the regulation of a drug concerns the good manufacturing practices (GMP), these GMP are detailed in an EMA document of 2001 updated in 2012 which applies to all human drugs including vaccines [5]. These GMPs concern, among other things and for preclinical studies, (see Annex I of the document [5]), the assessment of environmental risks, the characterization of the product and raw materials, their control and stability, manufacturing methods, pharmacology (mode

of action), toxicity, carcinogenicity, reproductive and embryo/fetal toxicity, pharmacokinetics, pharmacodynamics (modification of physiology by the drug), efficacy and product safety.

The pharmacokinetics is the action of the organism on a drug, i.e. the fate of the drug, from its entry to its exit from the organism, the evolution according to time of its absorption, its bioavailability, its distribution, its metabolism and its excretion.

We will see that these absolutely new products have not undergone all these controls.

Regulatory status of mRNA vaccines

The regulation of mRNA vaccines at the federal (US-FDA), European (EMA) and international (WHO) levels is complex, unclear and contradictory. The anti-Covid mRNA vaccines are the first mRNA vaccines marketed and no specific regulations existed before the year 2020. It is therefore necessary to refer to previous more general regulations and try to find the paragraphs that may relate to them. To solve this regulatory problem, WHO published a draft guidance document on December 20, 2020, for the assessment of quality, safety, and efficacy of mRNA vaccines, which includes the manufacture and control of vaccines as well as their non-clinical evaluation [6]. WHO admitted that detailed information was not available for the production of COVID-19 modRNA vaccines. In addition, safety and efficacy controls for gene-based biologics were not standardized, and some details remained proprietary and were not publicly disclosed. Given these uncertainties, WHO felt that it was not possible to develop specific international guidelines or recommendations and that some regulatory flexibility was needed.

mRNA vaccines are not subject to regulation as gene therapy products

One might have thought *a priori* that mRNAs could be subject to the regulation of gene therapy products (GTP), to which they objectively correspond [7] ("*Gene therapy products are all products that mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered microorganisms.*"). But already in 2007 the FDA distinguished between DNA plasmid vaccines according to whether they were for the prophylaxis of an infectious disease or not: DNA plasmids without indication in infectious diseases were subject to the regulation of gene therapy products, DNA plasmid vaccines against infectious diseases were subject to a separate regulation [8] and in 2013 the FDA confirmed that the regulation of gene therapy products did not apply to vaccines against infectious diseases [9].

According to European Union (EU) legislation, RNA-based medicines can currently be classified into different regulatory statuses, depending, for vaccines, on their target (infectious disease or not) and, for other medicines, on the way they are obtained (chemically or biologically) [10]. This classification determines the controls and studies that must be carried out to obtain marketing authorizations. Thus, mRNA vaccines against infectious diseases are not classified as gene therapy products [6Section M9 2.1 b] and [11] whereas mRNA vaccines for the treatment of cancers are GTMPs (Gene therapy

medicinal products which are part of ATMPs, advanced therapeutic medicinal products), in fact mRNAs are GTMPs according to the CAT (Committee for Advanced Therapies) and must therefore undergo complete pharmacokinetic studies [12].

It is therefore surprising that Moderna and BioNTech expected to have their products regulated as gene therapies. Moderna, Inc. acknowledged in its Q2 2020 Securities and Exchange Commission (SEC) filing that "*currently, mRNA is considered a gene therapy product by the FDA*" [13]. Furthermore, BioNTech founder Ugur Sahin, in a 2014 article, stated "*One would expect the classification of an mRNA drug to be a biologic, gene therapy, or somatic cell therapy*"[14].

Thus, the status of Covid mRNA vaccines was not well understood by the manufacturers themselves.

What regulations are mRNA vaccines subject to?

The 2005 WHO guidelines [15] grant nucleic acid-based vaccines the status of vaccines *("antigens produced in vivo in the vaccinated host following administration of a live vector or nucleic acid or antigens produced by chemical synthesis in vitro* "). Thus Covid mRNA vaccines must comply with this international regulation concerning GMP (good manufacturing practices), in particular the demonstration of the purity and quality of the raw material; it is specified that a pharmacodynamic study may also extend to the pharmacology of an adjuvant and that distribution studies must be considered in the case of new formulations. When a new additive is to be used, for which toxicological data are not available, toxicity studies of the additive alone should first be performed and the results documented in accordance with the guidelines for new chemical entities.

For Europe it is the 2001 document amended in 2012 that applies for the EMA to evaluate these mRNA vaccines as all vaccines (see Title 1 "Definitions" [5]). This document requires the declaration of the conformity of the raw materials, the composition of the product, stability studies of the active substances, pharmacokinetic studies (and pharmacology, e.g. quantitative composition, description of the manufacturing process, raw materials not listed in a pharmacopoeia, identification and assay of the active substance, in vitro or in vivo test of biological activity if assaying in the finished product is not possible, (tolerable deviation of 5% in the content of the active substance) For a new excipient refer to M2 3.2.2.4 d). Pharmacokinetics includes the study of absorption, distribution, biotransformation and excretion; *"Pharmacokinetic studies are usually not required for vaccines. However, such studies might be applicable when new delivery systems are employed or when the vaccine contains novel adjuvants or excipients."* [16]. According to a 2016 document [17], for the EMA, the regulations should follow those of the WHO and among the consequences it is specified that *"Since vaccines in most cases are given to large numbers of healthy individuals, there is a need for a solid nonclinical safety evaluation."* For vaccines containing free DNA the EMA asks to refer to the 2008 document[18]. This document refers to DNA plasmid vaccines (without specifying whether they are intended for use against an infectious disease or not). The document mentions the nucleic acid vehicle: *"Delivery vehicles - such as liposomes - might be used for transfection of plasmids or expression vectors. These should be investigated in the same way as the liposomes and virosomes used for other medicinal products or vaccine delivery*." So in contradiction to the exclusion of infectious disease

vaccines from this regulation of gene products, they do seem to be subject to it here:*"Biodistribution studies should provide data on all organs, whether target or not, as recommended in annex A to the Note for guidance on repeated dose toxicity (CPMP/SWP/1042/99) and include investigation on GTMP persistence, mobilisation and shedding. Generally, for this purpose, data obtained from transgene/expression vector are sufficient. Observation time should cover persistence of signal (i.e. duration of transgene expression and activity) and include time-points for which there is no signal detection, if applicable. The dosing should mimic the clinical use with appropriate safety margins. Data collected in these studies might also contribute to the environmental risk assessment (ERA)."*

Why are mRNA vaccines excluded from the regulation of gene products?

According to Guerriaud and Kohli [10], *it is difficult to answer with certainty why vaccines against infectious diseases have been excluded. The definition [of vaccines] has not changed since 1975, a period when there was no "vaccine" against cancer* [5]: they are agents capable of producing active immunity against an infectious disease. At that time the only existing vaccines were against infectious diseases and the current definition of a vaccine is limited to an immunological drug against an infectious disease. Therefore, an anti-cancer drug can in no way be called a "vaccine". It should be noted that therapeutic AIDS vaccines based on lentiviruses and acting as gene therapies because they integrate into the genome have also been excluded from gene therapies. From a public health point of view, and knowing (see below) that the classification as a "vaccine" allows the vaccine mRNA to escape the stricter controls of GMPs, one could object that a product intended for a majority of the world's healthy population should be subject to more stringent regulation than a gene therapy product intended for a few rare people suffering from a rare disease or cancer (this time concerning millions of people). Moreover, according to the EMA [17], "*Since vaccines in most cases are given to large numbers of healthy individuals, there is a need for a solid nonclinical safety evaluation*."

Regulatory studies for GTMPs were thus avoided for mRNA vaccines

The EMA regulation that should be referred to for these products and which does not concern RNA but only DNA (because it was drafted in 2008 [19]) requires extensive studies on both the nucleic acid and the vector particle/delivery system that include biodistribution, dose study, potential target toxicity, identification of the target organ to obtain biological activity, research into integration in the genome ("even if this integration is unlikely") and transmission in the germ line, toxicity linked to the expression of structurally altered proteins, reproductive toxicity (ICH M3 regulation), repeated toxicity, excretion in the environment [20].

Concerning the US-FDA, one should refer to the CBER (Center for Biologics Evaluation and Research) guide in charge of regulating these products but which only issues non-binding recommendations [21] as well as to the 2013 instructions [22] which globally impose the same criteria as the EMA.

The anti-COVID-19 mRNA vaccines have escaped all these controls, although they are essential for a new formulation and a new principle of action.

Conclusion

There is therefore no scientific justification to support this exclusion of vaccine mRNAs from the strict control rules that should apply for gene products. This is all the more true since mRNA vaccines are destined to become widespread, as are mRNA therapies: it is to be feared that this exclusion creates a precedent that could also exclude mRNA therapies from strict controls. These safety controls are absolutely essential for this new technology, which presents risks of specific toxicity, integration in the genome, transmission in the germ line, toxicity linked to the expression of structurally altered proteins, reproductive toxicity, repeated toxicity and excretion in the environment [20].

Why hasn't the FDA really evaluated these vaccines unlike the EMA?

In 2021, senior FDA officials resigned because they felt excluded from key decisions on Covid vaccines[23]. According to leaked EMA documents, U.S. and EU government officials pressured European drug regulators to quickly approve Pfizer-BioNTech's COVID-19 vaccine, despite safety concerns [24]. The management of the Covid health crisis by the state military apparatus must be discussed in terms of its consequences and may explain this lack of control: the various measures in response to the Covid pandemic were considered in the USA (and perhaps elsewhere?) as countermeasures against a biological weapon that did not require any clinical trials or proof of safety or efficacy. See in this regard the explanation by Katherine Watt [25], a legal scholar, on the US HHS decision to designate the Covid pandemic as the Public Readiness and Emergency Preparedness (PREP) Act [26]. The PREP Act authorizes the Secretary of the Department of Health and Human Services to issue a PREP Act declaration. This declaration provides immunity from liability (except for willful misconduct) for claims: of losses caused by, arising out of, relating to, or resulting from the administration or use of countermeasures to diseases, threats, and conditions determined by the Secretary to constitute a present or credible risk of a future public health emergency to entities and persons involved in the development, manufacture, testing, distribution, administration, and use of countermeasures.

In France, too, the health crisis was managed by the military: the Conseil de Défense Sanitaire is responsible for "taking crisis decisions in the health field" [27][28]. The existence of this state body is not defined either in the law or in the Constitution [29].

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